Nifedipine Reduces the Incidence of Myocardial Infarction and Transient Ischemia in Patients Undergoing Coronary Bypass Grafting

Rainald Seitlberger, MD; Werner Zwölfer, MD; Sebastian Huber, MD; Severin Schwarzacher, MD; Thomas M. Binder, MD; Friedrich Peschl, MD; Josef Spatt, MD; Christoph Holzinger, MD; Bruno Podesser, BS; Peter Buxbaum, MD; Heinz Weber, MD; and Ernst Wolner, MD

A randomized study was performed on 104 patients undergoing elective coronary artery bypass grafting to examine whether the infusion of nifedipine (n=53) reduces the incidence of perioperative myocardial ischemia and necrosis in the early postoperative period. Continuous hemodynamic and three-channel Holter monitoring was performed for 24 hours and serial assessment of serum enzymes and 12-lead electrocardiography were performed for 36 hours postoperatively. Nifedipine (minimum dose, 10 μg/kg/hr for 24 hours) was applied from the onset of extracorporeal circulation. The control group (n=51) received nitroglycerin (minimum dose, 1 μg/kg/min for 24 hours). Using the combined analyses of electrocardiography and Holter recordings, myocardial ischemia was defined as being either a transient ischemic event (TIE), transient coronary spasm (TCS), or myocardial infarction (MI). The two groups did not differ with respect to preoperative New York Heart Association classification, age, history of myocardial infarction, extracorporeal circulation and aortic cross-clamp time, number of distal anastomoses, or systemic and pulmonary hemodynamics. The incidence of perioperative myocardial ischemia was substantially lower in the nifedipine than in the nitroglycerin group [TIE: three of 53 patients (6%) versus nine of 50 patients (18%), p<0.001; MI: two of 53 patients (4%) versus six of 50 patients (12%), p<0.001; and TCS: none of 53 patients (0%) versus two of 50 patients (4%), p=NS]. In addition, the infusion of nifedipine led to a much lower extent of perioperative myocardial necrosis in comparison to the nitroglycerin group as estimated by postoperative peak values of creatine kinase (288.6±32.3 versus 440.6±76.0, p<0.01) and creatine kinase-MB (9.7±1.1 versus 26.0±6.1, p<0.01). In conclusion, perioperative infusion of nifedipine reduces the incidence of transient myocardial ischemia and myocardial infarction as well as the extent of myocardial necrosis in patients undergoing elective coronary bypass procedures compared with a control group receiving nitroglycerin. (Circulation 1991;83:460–468)

The perioperative phase in patients undergoing coronary artery bypass graft surgery (CABG) represents a very critical period. Apart from the quality of the surgical procedure itself, the outcome also depends on the quality of perioperative management, including adequate intraoperative myocardial protection.

Although perioperative mortality in elective procedures has reached a remarkably low level,1–3 the incidence of perioperative myocardial ischemia, such as myocardial infarction or transient myocardial ischemia, is still relatively high.4–8 Therefore, pharmacological interventions that decrease the incidence of perioperative myocardial ischemia may further improve short- and long-term results of coronary bypass surgery. Although controversial results have been reported regarding the anti-ischemic potency of nitroglycerin in the perioperative setting,9,10 the β-blocker propranolol11 seems ineffective in decreasing intraoperative or postoperative myocardial ischemia in patients undergoing coronary bypass surgery.
However, relatively little is known about the effect of calcium channel antagonists under these conditions.

Various clinical and experimental studies show that the calcium channel antagonist nifedipine acts as a coronary and peripheral vasodilator and is capable of reducing the incidence of myocardial ischemic events.\textsuperscript{12-14} As an adjunct to cardioplegia, nifedipine demonstrated a beneficial effect on myocardial adenine nucleotide metabolism during ischemia and reperfusion under experimental conditions.\textsuperscript{15} Clark et al\textsuperscript{16} demonstrated that the addition of nifedipine to a cardioplegic solution in patients undergoing various types of cardiac surgery procedures improved the postischemic cardiac performance and decreased the incidence of myocardial damage as defined by postoperative pyrophosphate scan. However, this study was performed on a specially selected group of high-risk patients with low cardiac indexes and decreased ejection fractions and could not show a beneficial effect of nifedipine on the incidence of Holter monitoring-assessed perioperative myocardial ischemia.

We recently demonstrated that postoperative infusion of nifedipine decreases the incidence of early postoperative myocardial infarction but has no effect on the prevalence of transient myocardial ischemia.\textsuperscript{17} In the present study, nifedipine was continuously infused from the onset of extracorporeal circulation to evaluate its anti-ischemic potency during the early postoperative period. A continuous infusion of nitroglycerin was performed in the control group to avoid significant hypertensive attacks, which by itself may trigger the occurrence of myocardial ischemia. Myocardial ischemia was detected by Holter monitoring and serial assessment of changes in electrocardiographic and serum enzyme levels.

**Methods**

The study was performed on 104 patients undergoing elective CABG. Patients with unstable angina, preoperative left or right bundle branch block, additional surgical or redo procedures, or a rethoracotomy due to excessive postoperative bleeding were excluded from the study. The patients were randomly assigned to nitroglycerin (control, n=51) or nifedipine (n=53). Informed consent was required for each patient before entering the study. The last medications (nitrates, \( \beta \)-blockers, or calcium antagonists) were given to the patients on the evening before surgery.

Premedication with 2 mg flunitrazepam p.o. was given about 1 hour before arrival in the operating theater. Anesthesia was then induced with etomidate 0.2–0.3 mg/kg, fentanyl 0.005–0.007 mg/kg, and diazepam 0.1–0.3 mg/kg. Before intubation, pancuronium 0.1 mg/kg was administered. Anesthesia was maintained with \( \text{O}_2 \)-\( \text{N}_2 \text{O} \), fentanyl, diazepam, and pancuronium; artificial ventilation was performed throughout the surgery and for at least 6 hours afterward at a rate of 12 breaths/min and a tidal volume of 10–12 ml/kg.

St. Thomas Hospital cardioplegic solution was used for myocardial protection during ischemia and given via the aortic root in addition to systemic hypothermia (29\( ^\circ \)C rectal temperature) and topical cooling. Patients assigned to the nifedipine group had continuous nifedipine infusion (minimum dose, 10 \( \mu \)g/kg/hr) from the onset of extracorporeal circulation until 24 hours after aortic cross-clamp time. During the same period of time, patients assigned to the control group had continuous nitroglycerin infusion (minimum dose, 1 \( \mu \)g/kg/min). The infusion rate was increased in both groups in case of postoperative hypertension (>90 mm Hg mean arterial pressure). Plasma levels of nifedipine were assessed 12 hours after the onset and immediately before the end of the nifedipine infusion. In all nifedipine-treated patients, the plasma levels were above the minimum therapeutic level of 10 ng/ml (range, 15–33 ng/ml). No case of nifedipine- or nitroglycerin-induced severe hypotension was encountered.

**Hemodynamic Measurements**

Before induction of anesthesia, a radial artery cannula and a Swan-Ganz catheter were inserted percutaneously into the pulmonary artery via the jugular vein for continuous arterial and pulmonary artery pressure recordings. Pulmonary artery wedge, central venous, and left atrial pressures recorded via a catheter inserted during surgery as well as cardiac output (Edwards 9520A thermodilution computer) were assessed immediately before surgery (except left atrial pressure) and 1, 8, 16, and 24 hours after aortic cross-clamp time. From these data, pulmonary arterial resistance (PAR), systemic arterial resistance (SAR), and cardiac index (CI) were calculated using standard formulas.

**Holter Monitoring and Electrocardiographic Recordings**

Assessment of perioperative electrocardiographic changes was performed by two methods.

First, continuous three-channel Holter monitoring was performed postoperatively using Marquette Holter recorders (series 8500, Milwaukee, Wisc.). Monitoring began 2 hours after aortic cross-clamp time at the intensive care unit and lasted 24 hours. The electrodes were placed so that channels one through three approximated electrocardiographic leads V\(_2\), V\(_5\), and aVF, respectively. All tapes were evaluated by the same investigator without knowledge of the patient's group assignment for ST segment elevations and depressions and for the incidence of ventricular arrhythmias, such as ventricular premature complexes (VPCs), ventricular couplets (VCs), and ventricular tachycardia (three or more VPCs in succession at a rate between 100 and 200 cycles/min) on a semiautomatic basis using a Marquette Laser Holter XP device (Milwaukee).

Second, 12-lead electrocardiographic recordings were performed shortly before and repeatedly for the first 36 hours after surgery (parallel to enzymatic
measurements) as well as every other day until postoperative day 10.

Four different forms of perioperative myocardial ischemia were defined by the combined analysis of electrocardiography and Holter recordings using the following criteria.

**Transient ischemic event.** A transient ischemic event (TIE) was considered a horizontal or downsloping ST segment depression of 1 mm or less and lasting at least 1 minute measured 60–80 msec from the J point in at least one Holter channel with no signs of evolving myocardial infarction.

**Transient coronary spasm.** A transient coronary spasm (TCS) was considered a monophasic ST segment elevation in at least one Holter channel without a Q wave in respective electrocardiographic leads and a shift of the ST segment-to-R wave ratio toward higher ST segments. If ST segment elevations did not match these criteria or those for myocardial infarction, other causes, such as postoperative pericarditis, were assumed.

**Myocardial infarction.** A myocardial infarction is defined as persistent typical ST segment elevation of 2 mm or more measured 60–80 msec from the J point in at least one Holter channel and development of a new Q wave (>0.04 seconds in duration and more than one fourth of the following R wave in amplitude) in the corresponding 12-lead electrocardiography after 10 days and/or during the 36-hour observation period after surgery, or persistent negative coronary T wave of more than 3 mm in 12-lead electrocardiography during the 36-hour postoperative observation period and/or 10 days after surgery without the occurrence of a new Q wave.

**Biochemical Analysis**

Creatine kinase (CK), the MB-isoenzyme of CK (CK-MB), lactate dehydrogenase (LDH), glutamate-oxaloacetate-transaminase (GOT), and glutamate-pyruvate-transaminase (GPT) were assessed immediately before surgery and 1, 2, 4, 6, 8, 12, 16, 20, 24, and 36 hours after aortic cross-clamp time using enzymatic fluorometric methods.

**Statistical Analysis**

Data in all tables are given as mean±SD. The raw data for each point in time and the peak value of each parameter within a patient were used for the analysis. An unpaired t test was performed to compare groups of data. In addition, the Wilcoxon rank sum test was performed on each parameter. Standard \( \chi^2 \) was used for comparison of baseline categorical (anumeric) factors and the incidence of ischemic events in the two treatment groups.

For the repeated hemodynamic and enzyme data, an analysis of variance (ANOVA) was performed with nifedipine versus nitroglycerin as the grouping factor and time as the within-group factor. Statistical comparison of values at different points in time with each other was performed using the Bonferroni t test. The level of significance for all tests was set at less than 0.05.

### Table 1. Preoperative Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nifedipine</th>
<th>Nitroglycerin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Male (%)</td>
<td>41 (77)</td>
<td>37 (73)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>12 (23)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61±8</td>
<td>60±7</td>
</tr>
<tr>
<td>One-vessel disease (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Two-vessel disease (%)</td>
<td>11 (21)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Three-vessel disease (%)</td>
<td>41 (77)</td>
<td>35 (69)</td>
</tr>
<tr>
<td>Left main stenosis (%)</td>
<td>14 (26)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Anterior/lateral myocardial infarction (%)</td>
<td>9 (17)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Posterior myocardial infarction (%)</td>
<td>11 (21)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>NYHA functional class (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>7 (13)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>III or IV</td>
<td>46 (87)</td>
<td>42 (82)</td>
</tr>
<tr>
<td>Preoperative therapy (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single drug</td>
<td>11 (21)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Double drug</td>
<td>27 (51)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Triple drug</td>
<td>15 (28)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>22 (42)</td>
<td>25 (50)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.

### Results

Tables 1 and 2 show clinical and surgical data of all patients considered to be of prognostic importance for perioperative morbidity. No significant differences were detected by either the t test or the Wilcoxon test for continuous variables between the nifedipine (average dose, 14 μg/kg/hr) and the nitroglycerin group with regard to clinical data (Table 1), such as severity of coronary artery disease, preoperative New York Heart Association classification, or therapeutic regimens and surgical data (Table 2), such as aortic cross-clamp time, bypass time, number of distal anastomoses, and number of internal mammary artery grafts.

### Table 2. Surgical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nifedipine</th>
<th>Nitroglycerin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>ACC time (min)</td>
<td>55±24</td>
<td>53±18</td>
</tr>
<tr>
<td>ECC time (min)</td>
<td>112±45</td>
<td>106±32</td>
</tr>
<tr>
<td>Grafts/patient (n)</td>
<td>3.52</td>
<td>3.38</td>
</tr>
<tr>
<td>Two grafts/patient (%)</td>
<td>9 (17)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Three grafts/patient (%)</td>
<td>19 (36)</td>
<td>24 (47)</td>
</tr>
<tr>
<td>Four grafts/patient (%)</td>
<td>15 (28)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Five grafts/patient (%)</td>
<td>8 (15)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Six grafts/patient (%)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IMA grafts (n)</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Endarterectomy (n)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

ACC, aortic cross clamp; ECC, extracorporal circulation; IMA, internal mammary artery.
TABLE 3. Hemodynamic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>1 hr</th>
<th>8 hr</th>
<th>16 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>NIT</td>
<td>N</td>
<td>NIT</td>
<td>N</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66.9±13.6</td>
<td>69.9±14.7</td>
<td>88.2±17.3</td>
<td>95.9±14.9*</td>
<td>93.0±15.7</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>78.7±10.0</td>
<td>81.7±13.3†</td>
<td>64.5±11.8</td>
<td>68.0±11.1†</td>
<td>74.1±9.5</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>...</td>
<td>...</td>
<td>9.3±3.7</td>
<td>9.1±3.2</td>
<td>8.7±2.9</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>8.5±3.5</td>
<td>8.6±3.0</td>
<td>7.9±4.2</td>
<td>8.0±2.5</td>
<td>7.9±3.2</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>18.0±5.3</td>
<td>16.7±3.5</td>
<td>15.7±4.7</td>
<td>16.2±4.5</td>
<td>16.0±3.8</td>
</tr>
<tr>
<td>Pulmonary arterial resistance (U)</td>
<td>4.5±1.2</td>
<td>3.5±1.1*</td>
<td>3.6±1.2</td>
<td>3.1±1.2</td>
<td>3.9±0.9</td>
</tr>
<tr>
<td>Systemic arterial resistance (U)</td>
<td>19.4±5.8</td>
<td>17.3±5.6</td>
<td>15.0±5.9</td>
<td>13.2±5.7</td>
<td>17.8±5.8</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.3±0.6</td>
<td>2.7±0.7†</td>
<td>2.6±0.8</td>
<td>3.0±0.8</td>
<td>2.5±0.7</td>
</tr>
</tbody>
</table>

N, nifedipine group (n=53); NIT, nitroglycerin (control) group (n=50); U, arbitrary unit.
*Value differs significantly from that for N group (p<0.01).
†Value differs significantly from that for N group (p<0.05).

Early mortality (defined as death occurring during hospitalization or within 30 days after surgery) was 2% in both groups (one patient per group). One patient with a preoperative ejection fraction of 20% (nitroglycerin group) died during surgery due to left ventricular failure. The autopsy revealed patent grafts and histological signs of multifocal myocardial necrosis not related to the surgical procedure; consequently, he was not classified as having perioperative myocardial infarction. Therefore, all data related to perioperative hemodynamics, biochemical analysis, and detection of ischemia in the nitroglycerin group were calculated for 50 patients only. The other patient (nifedipine group) died 20 days after surgery due to a sternal infection including mediastinitis, septicemia, and subsequent multiorgan failure. In this case, perioperative myocardial infarction was ruled out at the autopsy, and the perioperative study data were included in the analysis.

Hemodynamics

Table 3 depicts preoperative and postoperative hemodynamic parameters for both groups. ANOVA demonstrated no significant group differences for any assessed hemodynamic parameter.

Preoperative pulmonary vascular resistance was higher and cardiac index was lower in the nifedipine group. At the end of the observation period, however, cardiac index was similar in both groups, and pulmonary resistance was even lower in the nifedipine group. Preoperatively and at 1 hour after aortic cross-clamp time, mean arterial pressure was slightly higher in the nifedipine group, whereas left atrial pressure was higher in the nitroglycerin group 24 hours after aortic cross-clamp time. These data indicate that the pressure-lowering effect of the applied nifedipine dosages appears negligible and obviously does not cause hemodynamic problems during the postoperative period. The faster restoration of the cardiac index and the lower postoperative left atrial pressure in the nifedipine group demonstrate the protective effect of this drug during ischemia and/or reperfusion.

Myocardial Ischemia and Arrhythmias

All patients with TIEs, as defined by the combined Holter monitoring and electrocardiographic analysis, are listed in Table 4 with regard to number, total duration, and maximal observed increase in heart rate during the event. A substantial increase in heart rate during transient ischemia was observed in every patient independent of group assignment and demonstrates its hemodynamic significance.

Table 5 summarizes the data relating to myocardial ischemia and arrhythmias. The incidence of TIE [three of 53 patients (6%) versus nine of 50 patients (18%)] and perioperative myocardial infarction [two of 53 patients (4%) versus six of 50 patients (12%)] was significantly higher in the nitroglycerin group.
than in the nifedipine group. Among the patients with perioperative myocardial infarction, two (one in each group) were classified as having non-Q wave myocardial infarction. History of preoperative myocardial infarction or surgical data such as aortic cross-clamp time, bypass time, or number of distal anastomoses had no influence on the occurrence of perioperative TIE or myocardial infarction. TCS was detected in two patients assigned to the nitroglycerin group.

There was a tendency toward a lower incidence of VPC in the nifedipine group compared with the nitroglycerin group. Due to the skewness of these data, however, this difference did not reach statistical significance. The prevalence of VCs and ventricular tachycardia was similar in each group.

Myocardial Enzymes

Figure 1 depicts perioperative serum levels of the cardiосpecific enzyme CK-MB. ANOVA demonstrated an overall significant difference between the two groups (p<0.01).

The increase in the CK-MB levels during the first 4–6 hours after aortic cross-clamp time in both groups indicated a comparable extent of myocardial necrosis due to the surgical procedure itself. However, substantial differences in CK-MB levels were observed during the period as much as 36 hours after aortic cross-clamp time. Whereas CK-MB levels actually decreased in the nifedipine group, a substantial increase was observed in the nitroglycerin group. The difference between both groups was significant 12–36 hours after aortic cross-clamp time.

In addition, peak values for CK, CK-MB, LDH, and GOT were much higher in the nitroglycerin group (Table 5). However, peak GPT levels were similar in each group (Table 6). With regard to patients without any perioperative ischemic event (including TIE, MI, and TCS), peak levels of CK-MB were significantly lower in the nifedipine group, whereas no differences were observed for CK, LDH, GOT, and GPT levels.

![Figure 1](image-url)

**Figure 1.** Bar graph of serum creatine kinase–MB levels before surgery (pOP) and for 36 hours after opening of the aortic cross clamp. MB, MB-isoenzyme of creatine kinase; control, nitroglycerin group (n=50); nifedipine, nifedipine group (n=53). Data are given as mean±SEM. **Value differs significantly from that for nifedipine group (p<0.01).
Because only two patients in the nifedipine group but six patients in the nitroglycerin group developed signs of perioperative myocardial infarction, enzyme levels of this subgroup were not statistically analyzed for the two groups. On average, CK and CK-MB peak levels in these patients were twice as high compared with peak values of all the patients in the study, indicating a good correlation between electrocardiography and enzyme data. No significant differences were observed between groups of patients with TIE and between patients with or without TIE, regardless of which group they had been assigned to.

Discussion

Since the common use of hypothermic cardioplegia during cardiac surgery, myocardial preservation during the ischemic period has markedly improved and perioperative mortality has reached a remarkably low level, even in selected groups of patients with severely compromised myocardial function and high-risk profiles. However, the incidence of perioperative myocardial ischemia, preferentially expressed as the occurrence of new myocardial infarction, remains significantly higher than the mortality rate, especially in patients undergoing elective CABG procedures. The widespread use of PTCA as an alternate method for myo-cardiac revascularization and its comparably early success rate constitute a further challenge for the cardiac surgeon to minimize the incidence of any relevant perioperative complication, especially myocardial ischemia.

Because the effectiveness of myocardial protection during extracorporeal circulation almost eliminates significant ischemic damage to the myocardium, therapeutic measures that intend to decrease the incidence of perioperative myocardial ischemia should focus on the early reperfusion period in which myocardial perfusion primarily relies on patency and flow capacity of the bypass grafts.

Based on the results of postoperative Holter monitoring and the serial assessment of 12-lead electrocardiograms and myocardial enzymes, the present study provides evidence that continuous intraoperative and postoperative infusions of the calcium channel blocker nifedipine significantly decreases the incidence and extent of myocardial ischemia and necrosis after elective coronary bypass procedures. Since the incidence of perioperative hypertensive periods in patients undergoing coronary bypass procedures is relatively high, a continuous infusion of nitroglycerin was performed in the control group to achieve systemic arterial pressure values comparable to the nifedipine group throughout the observation period. This protocol avoided the necessity for uncontrolled bolus application or short-term infusion of various drugs such as clonidine, β-blockers, or nitropreside in the case of sudden hypertensive attacks, which may have also affected the incidence of myocardial ischemia.

However, a possible ischemic or anti-ischemic potency of the continuous nitroglycerin infusion limits the definition of the nitroglycerin group as a true control group. The anti-ischemic efficacy of nitroglycerin in this clinical setting of coronary bypass surgery is controversial and has yet to be defined in a randomized study. Thomson et al9 used a lower dose than we used (0.5 versus 1.0 μg/kg/min) and were unable to demonstrate a beneficial effect of nitroglycerin on the incidence of intraoperative myocardial ischemia as defined by continuous Holter monitoring. However, they did not assess the efficacy of nitroglycerin during the reperfusion period.

In contrast, Coriat et al11 reported that prophylactic infusion of nitroglycerin does prevent perioperative electrocardiographic changes in a nonrandomized study in patients undergoing coronary bypass surgery. However, the incidence of ischemia in their study appeared to be related to episodes of systemic hypertension. Because the incidence of perioperative myocardial ischemia (transient ischemia or myocardial infarction) in our nitroglycerin group was similar to true control groups in various other studies, it appears unlikely that nitroglycerin had any significant ischemic or anti-ischemic effect in this setting that would not justify designation of the nitroglycerin group as a control group.

Clinically, the most valuable finding of this study was the markedly lower incidence of perioperative myocardial infarction after nifedipine infusion compared with the nitroglycerin group (4% versus 12%). Apart from perioperative mortality, perioperative myocardial infarction represents the most significant

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>All patients</th>
<th>Patients without ischemia</th>
<th>Patients with TIE</th>
<th>Patients with MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (n=53)</td>
<td>NIT (n=50)</td>
<td>N (n=48)</td>
<td>N (n=3)</td>
</tr>
<tr>
<td>CK</td>
<td>288.6±141.2</td>
<td>440.6±250.9*</td>
<td>243.5±68.4</td>
<td>361.3±75.5</td>
</tr>
<tr>
<td>CK-MB</td>
<td>9.7±4.5</td>
<td>0.9±2.0*</td>
<td>9.0±3.9</td>
<td>10.7±5.0</td>
</tr>
<tr>
<td>LDH</td>
<td>345.6±83.2</td>
<td>453.6±162.3†</td>
<td>341.4±82.7</td>
<td>354.7±51.9</td>
</tr>
<tr>
<td>GOT</td>
<td>27.4±10.2</td>
<td>52.1±49.4*</td>
<td>26.2±9.5</td>
<td>36.0±18.5</td>
</tr>
<tr>
<td>GPT</td>
<td>15.7±5.3</td>
<td>19.3±7.4</td>
<td>15.7±5.4</td>
<td>13.7±3.2</td>
</tr>
</tbody>
</table>

TIE, transient ischemic events; MI, myocardial infarction; N, nifedipine group (n=53); NIT, nitroglycerin (control) group (n=50); CK, creatine kinase; CK-MB, MB-isoenzyme of CK; LDH, lactate dehydrogenase; GOT, glutamate-oxalacetate-transaminase; GPT, glutamate-pyruvate-transaminase.

*Value differs significantly from that for N group (p<0.01).
†Value differs significantly from that for N group (p<0.05).
complication following bypass surgery. Its accurate diagnosis in the operative setting, however, still causes profound methodological problems, which explain the high variance of 2–25% in the prevalence of perioperative myocardial infarction.1–6,18,19 For example, the diagnosis of myocardial infarction solely through the occurrence of a new Q wave lacks sensitivity as well as specificity even in combination with enzyme analysis and may underestimate the actual perioperative infarction rate.4,20

The diagnostic criteria for myocardial infarction in this study were based on the combined analysis of repeated electrocardiography and continuous Holter recordings and required the existence of a persistent ST segment elevation of more than 2 mm before the development of a new Q wave in the corresponding lead. In addition, a negative coronary T wave of more than 3 mm persisting throughout the 10-day observation period was also classified as myocardial infarction. This approach may explain that the incidence of myocardial infarction in the nitroglycerin group was rather high (12%) and coincides more closely with the 12–25% incidence of myocardial infarction in studies using additional diagnostic methods with presumably high sensitivity and specificity for myocardial infarction such as myocardial uptake of technetium-99m pyrophosphate on a scintigram or ventriculography for detection of functional changes.5,18,19

Conflicting reports have been published about the diagnostic accuracy of serum enzymes for the detection of myocardial infarction. Although CK-MB release seems to be the most reliable biochemical indicator for perioperative myocardial infarction, the lack of a generally accepted cutoff value (defined as peak activity or total quantity) and the interpatient variability of CK-MB levels compose its diagnostic sensitivity.21,22 Consequently, we did not include enzyme levels as an independent diagnostic parameter for defining myocardial infarction. Nevertheless, both CK and CK-MB levels were markedly higher in patients with perioperative myocardial infarction assessed by the combined analysis of electrocardiography and Holter monitoring recordings (see “Methods”) compared with patients with either a noneventful postoperative course or only transient ischemic events. In addition, patients treated with nifedipine demonstrated much lower CK-MB levels. This remained true when those with perioperative myocardial ischemia were excluded from analysis. Given the assumption that serum enzyme levels reflect, at least to a certain degree, the amount of damaged myocardial tissue,21,23 these data indicate that the tissue protective potency of nifedipine is capable of decreasing the extent of myocardial necrosis independent of any detectable anti-ischemic effect.

Although the clinical significance of perioperative myocardial infarction as a predictor of long-term operative success rates is well recognized,24 the predictive value of perioperative, transient ischemic events during surgery has yet to be elucidated. Although our study did not address this issue, it clearly demonstrates that continuous intraoperative and postoperative infusion of nifedipine effectively decreases the incidence of transient myocardial ischemia after bypass surgery. These results markedly differ from data of a previously published study17 in which infusion of nifedipine was started at 2 hours after the onset of the reperfusion period. In this study, nifedipine slightly reduced the incidence of early postoperative myocardial infarction but was unable to affect the incidence of perioperative transient myocardial ischemia or transient coronary spasm. Therefore, the potent anti-ischemic efficacy of the intraoperative and postoperative infusions of nifedipine in the present study emphasizes the significance of the early reperfusion period for the development of postoperative myocardial ischemia after bypass surgery.

This conclusion is based on the analysis of postoperative ST segment changes as recorded by three-channel Holter monitoring. The sensitivity of this method for the detection of myocardial ischemic events is similar to the sensitivity of exercise electrocardiography.25 Only recently, however, was Holter monitoring introduced as an additional noninvasive method for the detection of ischemia during the early postoperative phase7,8 because certain difficulties exist in the interpretation of ST segment changes throughout the perioperative period: A number of technical and clinical factors such as electrode imbalance, temperature changes, history of myocardial infarction or postoperative pericarditis, or changes in the activity of the autonomic nervous system26,27 may affect the analysis. Because the specificity of the interpretation of ST segment changes as real ischemic events rely on various variables, we used strict diagnostic criteria that included the combined analyses of Holter recordings and 12-lead electrocardiography (see “Methods”). Although not free from methodological limitations, this noninvasive diagnostic approach may provide a reliable diagnostic tool for detection of perioperative myocardial ischemia.

The results of this study demonstrate the relatively high prevalence of postoperative transient ischemic events (19% in the nitroglycerin group) with a substantial variability in frequency and duration. This number is substantially lower than the 40% incidence of TIE recently reported in a study performed under similar conditions.7 However, the longer recording period (48 versus 24 hours in our study) and the inclusion of persistent ST segment elevations in their definition of transient myocardial ischemia may account for these differences. Persistent ST segment elevations of less than 3 mm were not attributed to myocardial ischemia in our study because they may stem from various accountable causes unrelated to ischemia, such as perioperative pericarditis.

In accordance with its effect on the incidence of perioperative myocardial infarction, nifedipine also significantly reduced the incidence of transient myocardial ischemia (6% versus 19%). Because patients
with TIE demonstrated no differences in enzyme levels compared with noneventful patients, the clinical value of a reduction in perioperative transient ischemia remains unclear. It is speculated, however, whether a lower incidence of "silent ischemia" during this period may also predict a lower incidence of graft closure and/or postoperative infarction during long-term follow-up, as has been shown for patients with coronary disease and variant or unstable angina.28,29

According to the diagnostic criteria designed to rule out ST segment variations not related to ischemia, two cases of transient coronary and/or graft spasm were documented in the nitroglycerin group. Although perioperative vasospasm appears to be a rare complication, several case reports have been published.30 However, the role of coronary and/or graft spasm as a possible cause of substantial perioperative myocardial ischemia has yet to be defined.31 With regard to this study, no increase in myocardial enzymes or signs for hemodynamic instability that may have indicated more severe myocardial ischemia were observed in either documented case. Due to the low incidence of transient coronary spasms, it was impossible to use any statistical analysis to answer the question as to whether nifedipine may have affected their occurrence. However, we cannot rule out that perioperative myocardial infarction observed in our patients was, at least in some cases, related to vasospasm. Consequently, the repeatedly documented efficacy of nifedipine in the treatment of coronary spasm32 may have also contributed to the significantly lower incidence of myocardial infarction in nifedipine-treated patients.

It seems very unlikely that differences between the two groups not accounted for in our analysis were responsible for the beneficial effect of nifedipine during the early postoperative period. All relevant clinical (e.g., age, sex, severity of coronary artery disease, history of myocardial infarction) and surgical (e.g., aortic cross-clamp time, bypass time, number of distal anastomoses) data that may predict the occurrence of perioperative myocardial ischemia were sufficiently matched between the groups and demonstrated no significant differences. Due to the comparable number of patients in each group with preoperative nifedipine treatment, the controversial nifedipine withdrawal phenomenon probably did not influence the results of our study.33 This assumption is confirmed by the fact that only three of the six patients with perioperative myocardial infarction in the nitroglycerin group received preoperative calcium blocker therapy, including only one on nifedipine.

There are several possible pathophysiological mechanisms that may explain the documented anti-ischemic efficacy of nifedipine in patients undergoing coronary bypass procedures. Since hemodynamic parameters indicative of changes in myocardial oxygen consumption, such as arterial pressure or heart rate, were similar in both groups, a possible oxygen-sparing effect of the calcium antagonist nifedipine cannot account for its anti-ischemic potency. More likely, nifedipine-induced mechanisms that act directly on the coronary vasculature and increase myocardial blood flow primarily in the subendocardium are responsible for the observed beneficial effect. This nifedipine effect has been observed even in low concentrations, which have no effect on arterial and, consequently, coronary perfusion pressure.12

Recent experimental and clinical studies suggest that an additional mechanism may account for the anti-ischemic nifedipine effects in the treatment of angina pectoris as well as in this perioperative study. Significant α2-mediated sympathetic coronary vasoconstriction is of special importance during various degrees of myocardial ischemia and under certain conditions, which lead to an activation of the sympathetic nervous system, such as stress, exercise, or anesthesia.34-36 Nifedipine has been shown to be a functional antagonist of α2-receptor-mediated sympathetic coronary vasoconstriction and thereby reduces coronary vascular resistance, even under conditions of severe myocardial ischemia.12,34 This functional antagonistic efficacy of nifedipine is certainly of clinical relevance during the early postoperative period, when a decrease in flow resistance distal to a graft anastomosis or an un bypassed borderline coronary stenosis may increase blood flow through bypass grafts and coronary arteries. This mechanism conceivably reduces the incidence and severity of regional myocardial ischemia and/or flow disturbances, which may otherwise induce clot formation and eventually lead to myocardial infarction.

Nifedipine has also been reported to prolong bleeding time, to significantly reduce primary and secondary platelet aggregation by inhibiting calcium transport across the cell membrane, and to inhibit the platelet response to thromboxane A2, an antithrombotic effect functionally comparable to that induced by aspirin.37,38 Although an antithrombotic potency is potentially of therapeutic significance in the prevention of ischemia after coronary bypass procedures, our data do not allow any conclusions as to whether this additional property of nifedipine played a major role in our investigation.

In conclusion, our randomized study with perioperative infusion of nitroglycerin in the control group and the calcium channel blocker nifedipine in the treatment group provides evidence that infusion of nifedipine is a potent measure for the prevention of perioperative myocardial infarction and transient ischemia. Because none of the patients investigated showed adverse side effects, such as severe hypotension, this investigation suggests that further study of nifedipine as a potentially effective therapeutic adjunct to the perioperative care of patients undergoing coronary bypass procedures would be highly warranted.

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Nifedipine reduces the incidence of myocardial infarction and transient ischemia in patients undergoing coronary bypass grafting.
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